Amsterdam, 18 September 2025
EMADOC-1700519818-2242426
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Gardasil 9

human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)

Procedure no: EMA/PAM/0000281431

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	25 August 2025	25 August 2025
☐	CHMP comments	8 September 2025	N/A
☐	Updated CHMP Rapporteur AR	11 September 2025	N/A
☒	CHMP outcome	18 September 2025	18 September 2025

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1. Introduction

On 23 June 2025, the MAH submitted a completed paediatric study for Gardasil 9, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that V503-076, A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9vHPV and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Commercially available vaccine formulations Gardasil 9 (9vHPV, MSD) and Spikevax (mRNA-1273, Moderna) were used in this clinical trial. Human Papilloma Virus (HPV) vaccine Gardasil 9 contains VLPs of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. SARS-CoV-2vaccine mRNA-1273 includes mRNA, which encodes S- protein from Wuhan strain.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• V503-076, A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9vHPV and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age.

The 9vHPV vaccine (V503) is an aluminum-adjuvanted recombinant protein vaccine prepared from the VLPs of the recombinant major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 and was shown to be efficacious clinical studies. The 9vHPV vaccine is currently indicated in many countries for the prevention of cervical, vulvar, vaginal, anal and head and neck cancers, and precancerous or dysplastic lesions, genital warts, and infection caused by the 9 HPV types targeted by the vaccine. The 9vHPV vaccine was initially licensed and recommended as a 3-dose vaccination series. It was subsequently approved for a 2-dose regimen in individuals 9 to 14 years of age (the main target population for vaccination) in many countries, including EU.

The Spikevax (mRNA-1273) received CMA in EU in January 2021 of a 2-dose regimen of the mRNA-1273 vaccine at the 100-µg dose level for persons ≥18 years of age was based on a clinical study (mRNA-1273-P301; NCT04470427), which demonstrated clinical efficacy in preventing symptomatic, laboratory-confirmed COVID-19 infection with an acceptable safety profile. The mRNA-1273 SARS-CoV-2 vaccine was studied in children 6 to 11 years of age (mRNA-1273-P204; NCT04796896). The study demonstrated a robust neutralizing antibody response after 2 doses of mRNA-1273 vaccine at the 50-µg dose level with a favourable safety profile, which was the basis for authorization for individuals aged 6 to 11 years of age from the European Commission on 02-MAR-2022.

Previous studies (V503-005, V503-007) have demonstrated that the concomitant use of the 9vHPV vaccine with other vaccines (ie, meningococcal, poliomyelitis, diphtheria, tetanus, and pertussis) routinely administered in this age group was well tolerated and did not interfere with antibody responses to any of the vaccines concomitantly administered. Concomitant administration of vaccines in this age group may help minimize the number of vaccination visits required and improve implementation of vaccination programs.

There are data available for SARS-CoV-2 mRNA vaccines co-administered with other vaccines in adult populations, but to date, no coadministration data for an mRNA COVID-19 vaccine has been generated in pediatric populations. At the time of initial authorization for mRNA COVID-19 vaccines in the pediatric population in MAY 2021, Advisory Committee on Immunization Practices (ACIP) noted the lack of available data and called for studies to generate safety and immunogenicity data on coadministration. Currently, the monovalent COVID-19 mRNA-1273 vaccine that was used in this study is no longer authorized for use in the US, though it remains authorized for use as a 2-dose primary series vaccination in the EU. The originally authorized mRNA-1273 vaccine has been adapted to target the most recent strains of the virus and 4 adapted mRNA COVID-19 vaccines are at the time of this CSR authorized for use in Europe.

2.3.2. Clinical study V503-076, A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9vHPV and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age

Description

This was a randomized, open-label, multicenter study to evaluate the safety and immunogenicity of a 2-dose regimen of 9vHPV vaccine, where the first dose was administered concomitantly with a first dose of a 2-dose regimen of mRNA-1273 vaccine versus nonconcomitant administration of 9vHPV and mRNA-1273 vaccines in boys and girls 9 to 11 years of age.

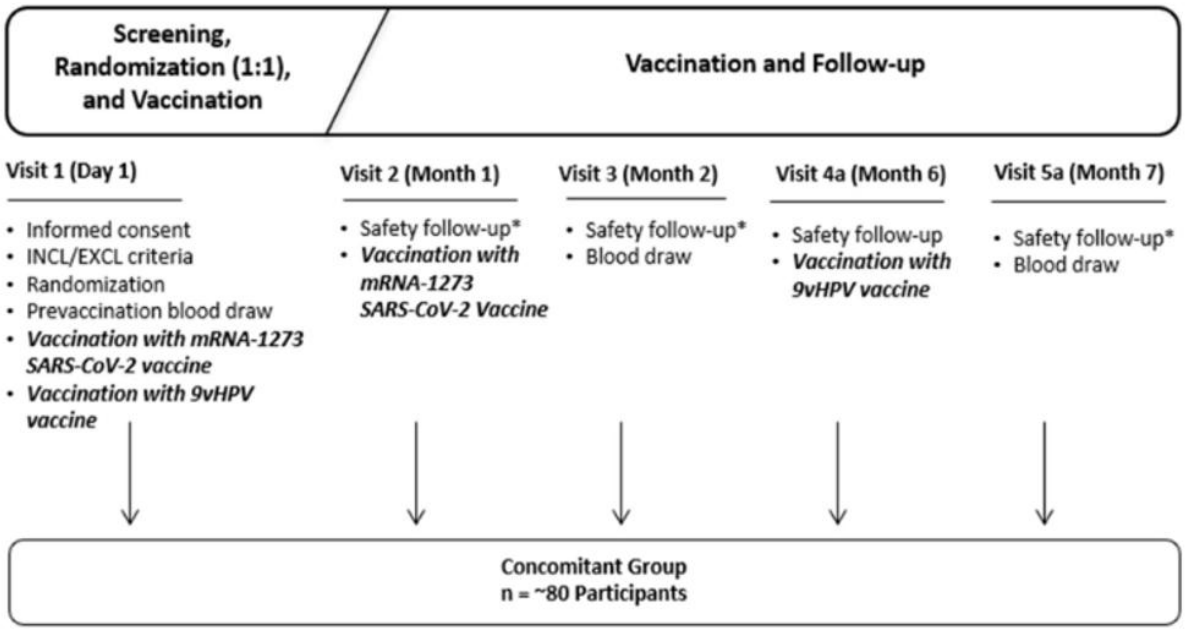
Originally, this study supposed to be hypothesis tested to demonstrate non-inferior immune responses when Gardasil 9 is co-administered with mRNA-1273. It was planned to recruit at least 400 individuals. With protocol amendment nr .3 (15.02.2023), the study became descriptive due to the early closure of enrolment. Therefore, this study was a descriptive study. No hypotheses were tested. The study was designed to enrol approximately 160 participants. Eligible participants were planned to be randomly assigned in a 1:1 ratio to 1 of the following groups:

• Concomitant Group: Participants were randomly assigned to receive their first dose of 9vHPV vaccine and first dose of mRNA-1273 vaccine on Day 1; they then received their second dose of mRNA-1273 vaccine at Month 1 and their second dose of 9vHPV vaccine at Month 6. Serum for anti-HPV antibodies was collected on Day 1 and Month 7, and serum for SARS-CoV-2 spike protein-specific binding antibody was collected on Day 1 and Month 2.

• Nonconcomitant Group: Participants were randomly assigned to receive their first and second doses of mRNA-1273 vaccine on Day 1 and at Month 1, respectively; they then received their first and second doses of 9vHPV vaccine at Months 2 and 8, respectively. Serum for anti-HPV antibodies was collected on Month 2 and Month 9, and serum for SARS-CoV-2 spike protein-specific binding antibody was collected on Day 1 and Month 2.

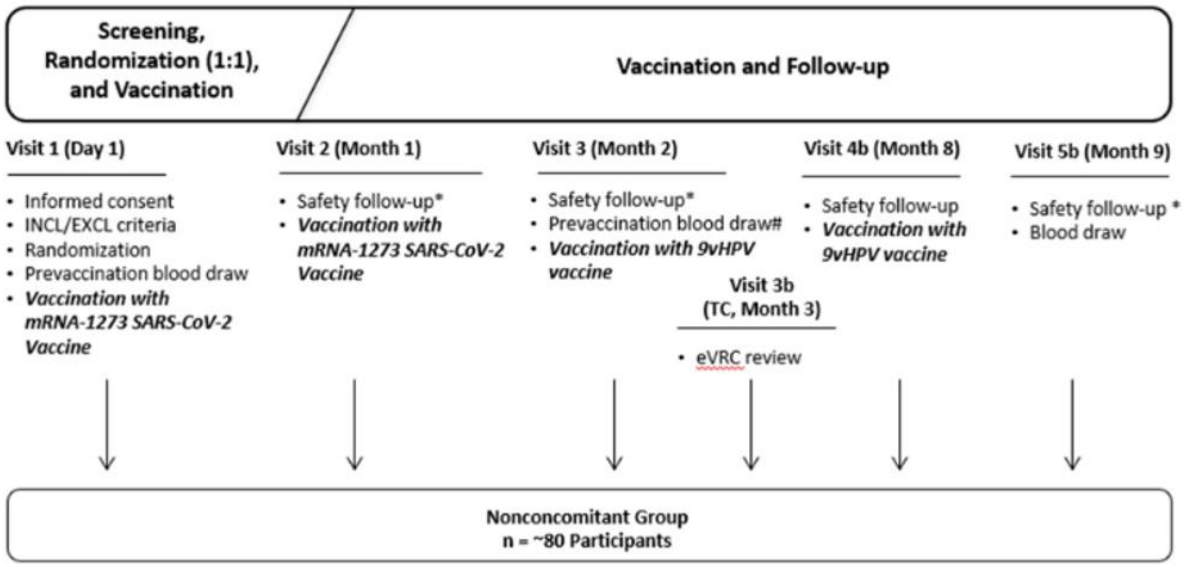
For both the concomitant and nonconcomitant groups, solicited AEs were collected Day 1 to Day 7 after each vaccination visit, and unsolicited AEs were collected Day 1 to Day 28 after each vaccination visit. SAEs, AESIs, and MAAEs were collected through the duration of participation in the study.

Figure 1 - Study Design for Concomitant Group



eVRC=electronic Vaccination Report Card; HPV=human papillomavirus; INCL/EXCL=Inclusion/Exclusion Criteria; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
* Including eVRC review

Figure 2 - Study Design for Nonconcomitant Group



eVRC=electronic Vaccination Report Card; HPV=human papillomavirus; INCL/EXCL=Inclusion/Exclusion Criteria; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; TC=telephone contact
* Including eVRC review
# Prevaccination blood draw for baseline anti-HPV antibody testing and SARS-CoV-2 Spike protein-specific binding antibody testing Postdose 2 of mRNA-1273 SARS-CoV-2 vaccine

Methods

Study participants

Key criteria for inclusion in the study included:

• Healthy individuals.

• Male or female 9 to 11 years of age, inclusive.

• Not yet had coitarche and did not plan on becoming sexually active during the vaccination period.

• Participant or participant's legally acceptable representative understands the study and risks involved with the study and voluntarily agrees to participate by providing documented informed consent.

• Agrees to provide study personnel with a primary telephone number.

• Participant or participant's legally acceptable representative can read, understand, and complete the eVRC.

A total of 165 participants were randomized and 162 participants were randomized and vaccinated across 18 study sites in the US. Of the165 participants randomized, 3 participants did not receive study intervention.

Table 1 - Treatments

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Concomitant Group	mRNA-1273 vaccine	mRNA* 50 µg per dose	0.25 mL per dose	IM	Single dose at Day 1 and Month 1	Test Product
Concomitant Group	9vHPV vaccine	HPV6/11/16/18/31/33/ 45/52/58 L1 VLP: 30/40/60/40/20/20/20/ 20/20 mcg per dose	0.5 mL per dose	IM	Single dose at Day 1 and Month 6	Test Product
Nonconcomitant Group	mRNA-1273 vaccine	mRNA* 50 µg per dose	0.25 mL per dose	IM	Single dose at Day 1 and Month 1	Test Product
Nonconcomitant Group	9vHPV vaccine	HPV6/11/16/18/31/33/ 45/52/58 L1 VLP: 30/40/60/40/20/20/20/ 20/20 mcg per dose	0.5 mL per dose	IM	Single dose at Month 2 and Month 8	Test Product

9vHPV=9-valent human papillomavirus; HPV=human papillomavirus; IM=intramuscular; IMP=Investigational Medicinal Product; mRNA=messenger ribonucleic acid; NIMP/AxMP=noninvestigational/auxiliary medicinal product; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; VLP=virus-like particle

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

* mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 virus (Moderna Inc., Cambridge, MA)

Table 2 - Objectives and Outcomes/Endpoints

Primary Objective	Primary Endpoint
• **Objective 1:** To evaluate the GMTs of antibodies to each of the 9vHPV vaccine types at 4 weeks Postdose 2 of a 2-dose regimen of 9vHPV vaccine, when the first dose of a 2-dose regimen of 9vHPV vaccine is administered concomitantly or nonconcomitantly with a first dose of a 2-dose regimen of mRNA-1273 vaccine.	• Serum antibody titers at 4 weeks Postdose 2 of 9vHPV vaccine measured by cLIA to each of the 9vHPV vaccine types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)
• **Objective 2:** To evaluate the GMCs of SARS-CoV-2 spike protein-specific binding antibody at 4 weeks Postdose 2 of a 2-dose regimen of mRNA-1273 vaccine, when the first dose of a 2-dose regimen of mRNA-1273 vaccine is administered concomitantly or nonconcomitantly with a first dose of a 2-dose regimen of 9vHPV vaccine.	• Serum antibody concentrations at 4 weeks Postdose 2 of mRNA-1273 vaccine measured by ECL assay specific to the SARS-CoV-2 spike protein
• **Objective 3:** To evaluate the safety and tolerability of 2-dose regimens of 9vHPV and mRNA-1273 vaccines where the first dose of each vaccine is administered concomitantly.	• Solicited injection-site AEs • Solicited systemic AEs • SAEs • Vaccine-related SAEs
Secondary Objectives	**Secondary Endpoints**
• **Objective:** For each of the Concomitant and Nonconcomitant Groups, to estimate percent seroconversion to each of the 9vHPV vaccine types at 4 weeks Postdose 2 induced by a 2-dose regimen of 9vHPV vaccine.	• Serum antibody titers at 4 weeks Postdose 2 of 9vHPV vaccine measured by cLIA to each of the 9vHPV vaccine types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)
• **Objective:** For each of the Concomitant and Nonconcomitant Groups, to estimate percent seroresponse at 4 weeks Postdose 2 induced by a 2-dose regimen of mRNA-1273 vaccine.	• Serum antibody concentrations at 4 weeks Postdose 2 of mRNA-1273 vaccine measured by ECL assay specific to the SARS-CoV-2 spike protein

CHMP's comment: the study design, objectives and endpoints are acceptable. Co-administration studies are often descriptive.

Sample size

Immunogenicity

This is an estimation study. There are no hypotheses to be evaluated. The expected total sample size is approximately 160 participants.

The study planned to enrol approximately 400 participants (200 per group) according to the Study Protocol nr.1 to be able to estimate non-inferior immune response. Given this sample size, the study would have at least 90% power to demonstrate the H1 and H2 hypotheses at an overall Type I error α=0.025 (1-sided). The achieved power corresponding to a sample size of 200 per group assuming all assumptions hold is 99.2%. As the study enrolment was stopped when 160 individuals were recruited, the study became an estimation study instead of the hypothesis tested study.

Sample Size and Power for Safety Analysis

The probability of observing at least 1 vaccine-related SAE depends on the number of participants vaccinated and the underlying incidence rate in the study population. In this study with 80 participants in each vaccination group, there is ≥0.90 probability of observing at least 1 vaccine-related SAE in a vaccination group if the incidence of a SAE is ≥2.84% (Table 3). If no vaccine-related SAE is observed among the approximately 80 participants in a vaccination group, this study will provide 97.5% confidence that the underlying incidence rate of vaccine-related SAE in that vaccination group is ≤4.51% (10 of every 222 individuals).

Table 3 - Probability of observing at least 1 vaccine-related serious adverse event in a group with 80 participants

Incidence Rate	Probability of ≥1 Participant Out of 80 With Vaccine-related SAE
2.84% (1 of every 35 participants)	0.90
3.68% (1 of every 27 participants)	0.95
8.27% (1 of every 12 participants)	0.99
SAE=serious adverse event	

Randomisation and blinding (masking)

Intervention allocation/randomization occur centrally using an IRT system. There were 2 study intervention arms. Participants were assigned randomly in a 1:1 ratio to the Concomitant Group and Nonconcomitant Group, respectively. This was an open-label study therefore, the Sponsor, investigator, and participant will know the vaccine administered.

Immunogenicity Assessments

Antibody to 9vHPV Vaccine Types Measured by Competitive Luminex Immunoassay

The 9-valent HPV cLIA was used as a primary method to evaluate antibodies specific for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in serum [Roberts, C., et al 2014]. The purpose of the assay is to detect these HPV antibodies before and after vaccination with the 9vHPV vaccine. The testing will be performed by Q Squared Solutions (California, USA). For the 9-valent HPV cLIA, HPV type-specific, yeast-derived VLPs are coupled to 9 distinct Luminex magnetic microspheres. Each VLP-coupled microsphere has its own distinct fluorescent dye that can be recognized by excitation with an infrared laser, allowing for the measurement of antibodies against multiple HPV types from a single test of an individual's serum. HPV type-specific monoclonal antibodies labeled with R-Phycoerythrin compete with an individual's serum antibodies for binding to the neutralizing epitopes of the VLPs. The fluorescent signal from the R-Phycoerythrin-labelled, type-specific monoclonal antibodies is inversely proportional to the anti-HPV antibody concentration of a sample. Antibody concentrations are derived from a standard curve, which is generated using a reference standard made from a pool of serum from individuals immunized against the 9 HPV vaccine types. A standard curve for each HPV vaccine type is calculated using a weighted 4 parameter logistic curve fit. Results are expressed as mMU/mL.

SARS-CoV-2 Spike Protein-specific Binding Antibody Measured by ECL Assay

PPD VSD in Richmond, VA, has developed and validated an ECL Method for the Detection of SARS-CoV-2 Spike, Nucleocapsid, and Receptor Binding Domain antibodies in human serum. The assay is based on the Meso-Scale Discovery technology, which employs disposable multispot microtiter plates. The validation study established the assay operating characteristics, evaluated the precision and ruggedness, and assessed the dilutional linearity, selectivity, and relative accuracy of the SARS-CoV-2 antigens. The SARS-CoV-2 ECL assay met the prespecified acceptance criteria and is considered

validated with regard to precision, ruggedness, relative accuracy, dilutional linearity, specificity, and selectivity.

Statistical Methods

Immunogenicity Analyses Population

The Per Protocol Immunogenicity (PPI) population served as the primary population for the analysis of immunogenicity relating to 9vHPV vaccination. The PPI population was HPV type-specific. The PPI population consisted of all randomized participants who:

1. Received all vaccinations planned within the context of the study with the correct dose of the 9vHPV vaccine and each vaccination visit has occurred within day ranges acceptable for statistical analysis.
2. Were seronegative by HPV-9 cLIA to the appropriate HPV type pre-9vHPV vaccination.
3. Had evaluable serology results based on serum sample collected within 21 to 49 days Postdose 2 of 9vHPV vaccination.
4. Had no protocol deviations that could interfere with the evaluation of participant's immune response to 9vHPV vaccination.

The mRNA-1273-PP population served as the primary population for the analysis of immunogenicity relating to mRNA-1273 vaccination. This population consisted of all randomized participants who:

5. Had received all vaccinations planned within the context of the study with the correct dose of mRNA-1273 and each vaccination visit has occurred within day ranges acceptable for statistical analysis.
6. Had evaluable serology results based on serum sample collected within 21 to 42 days Postdose 2 of mRNA-1273 vaccine.
7. Had no protocol deviations that could interfere with the evaluation of participant's immune response to mRNA-1273 vaccine.

Key Immunogenicity Analyses

Evaluation of primary and secondary objectives were performed separately for each immunogenicity parameter. Analysis of variance modelling was used. The response variable was the natural logarithm of the relevant antibody titers and an indicator variable representing the concomitant vaccination group was a fixed effect. Point estimates of the GMTs/GMCs and corresponding within-group 95% CIs as well as geometric mean ratio and corresponding 95% CI of the geometric mean ratio were derived from the estimate of the fixed effect.

Safety Analysis Population

Safety analyses were based on the APaT population, which included all 162 randomized participants who received at least 1 dose of study intervention according to the study intervention they received. This was the treatment group which they were randomized except for participants who received incorrect vaccination regimen for the entire vaccination period; such participants were included in the treatment group corresponding to the vaccination regimen actually received.

Key Safety Analyses

By-treatment group summaries of safety endpoints were provided in terms of treatment group-specific counts and proportions (or percent) of participants who were cases of particular safety endpoints. CIs of risk difference (difference in percent or proportions), when provided, were calculated using the M&N method.

Results

Participant flow

The disposition of participants was similar between the concomitant and nonconcomitant administration groups [Table 4Table 4]. Overall, a total of 165 participants were randomized, 3 participants did not receive study intervention, more than 78% of participants completed the study. The reasons for discontinuing either study intervention were lost to follow-up and withdrawal by parent/guardian.

Table 4 - Disposition of Participants (All Randomised Participants)

	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant		9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	82		83		165	
Vaccinated with						
mRNA-1273 Dose 1	81	(98.8)	81	(97.6)	162	(98.2)
mRNA-1273 Dose 2	78	(95.1)	78	(94.0)	156	(94.5)
9vHPV Dose 1	81	(98.8)	72	(86.7)	153	(92.7)
9vHPV Dose 2	67	(81.7)	66	(79.5)	133	(80.6)
Status for Trial						
Completed	66	(80.5)	64	(77.1)	130	(78.8)
Discontinued	16	(19.5)	19	(22.9)	35	(21.2)
Lost To Follow-Up	6	(7.3)	8	(9.6)	14	(8.5)
Randomized By Mistake Without Study Treatment	0	(0.0)	1	(1.2)	1	(0.6)
Withdrawal By Parent/Guardian	10	(12.2)	10	(12.0)	20	(12.1)
Status for Study Medication in Trial (9vHPV Vaccine)						
Started	81		72		153	
Completed	67	(82.7)	66	(91.7)	133	(86.9)
Discontinued	14	(17.3)	6	(8.3)	20	(13.1)
Lost To Follow-Up	6	(7.4)	5	(6.9)	11	(7.2)
Withdrawal By Parent/Guardian	8	(9.9)	1	(1.4)	9	(5.9)
Status for Study Medication in Trial (mRNA-1273 Vaccine)						
Started	81		81		162	
Completed	78	(96.3)	78	(96.3)	156	(96.3)
Discontinued	3	(3.7)	3	(3.7)	6	(3.7)
Lost To Follow-Up	1	(1.2)	1	(1.2)	2	(1.2)
Withdrawal By Parent/Guardian	2	(2.5)	2	(2.5)	4	(2.5)

If the overall count of participants is calculated and displayed in the first row of a section, then it is used as the denominator for the percentage calculation within the section. Otherwise, participants in population is used as the denominator for the percentage calculation.
Participants are included in the treatment group to which they are randomized.
9vHPV=9-valent human papillomavirus; mRNA=messenger ribonucleic acid.

Source: [P076V503: adam-adsl; adex]

Recruitment

This study was conducted at 38 centres in 1 country (USA). The recruitment lasted from 2022 to 2023. At 28-MAR-2022 was the first participant first visit, at 12-DEC-2023 last participants last visit and at 25-FEB-2025 last data was available. Study is completed.

Baseline data

Demographic characteristics of the study population were generally similar between concomitant and nonconcomitant administration (Table 5). Study populations median age was 10 years, about 2/3 were Whites and 1/3 Blacks. The study intended to recruit equally boys and girls, but girls were represented with a bit higher proportion (53 % vs. 47 %).

Table 5 - Participant Characteristics (All Randomised Participants)

	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant		9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	82		83		165	
Sex						
Male	39	(47.6)	38	(45.8)	77	(46.7)
Female	43	(52.4)	45	(54.2)	88	(53.3)
Age (Years)						
9	36	(43.9)	31	(37.3)	67	(40.6)
10	20	(24.4)	30	(36.1)	50	(30.3)
11	26	(31.7)	22	(26.5)	48	(29.1)
Mean	9.9		9.9		9.9	
SD	0.9		0.8		0.8	
Median	10.0		10.0		10.0	
Range	9 to 11		9 to 11		9 to 11	
Race						
Asian	1	(1.2)	0	(0.0)	1	(0.6)
Black Or African American	28	(34.1)	31	(37.3)	59	(35.8)
Multiple	0	(0.0)	2	(2.4)	2	(1.2)
White	53	(64.6)	48	(57.8)	101	(61.2)
Missing	0	(0.0)	2	(2.4)	2	(1.2)
Ethnicity						
Hispanic Or Latino	50	(61.0)	46	(55.4)	96	(58.2)
Not Hispanic Or Latino	32	(39.0)	37	(44.6)	69	(41.8)
Weight (kg)						
Participants with data	82		81		163	
Mean	44.87		44.75		44.81	
SD	14.71		15.16		14.89	
Median	40.80		43.80		41.70	
Range	25 to 90		19 to 98		19 to 98	
Height (cm)						
Participants with data	82		81		163	
Mean	141.86		142.64		142.25	
SD	11.98		10.83		11.40	
Median	143.95		142.00		142.50	
Range	106 to 168		117 to 164		106 to 168	
BMI (kg/m2)						
Participants with data	82		81		163	
Mean	22.17		21.61		21.89	
SD	6.55		5.64		6.10	
Median	20.23		20.27		20.27	
Range	14 to 55		13 to 38		13 to 55	

SD=Standard deviation.
9vHPV=9-valent human papillomavirus; BMI=body mass index; cm=centimeter; kg=kilometer; m2=square meter; mRNA=messenger ribonucleic acid.

Source: [P076V503: adam-adsl]

Table 6 - Numbers analysed

Received at least 1 9vHPV dose	**Concomitant vaccination N (%)**	**Separate vaccination N (%)**	**Total**
Safety population	81	81	162
9vHPV immunogenicity	81	72	153
HPV 6 Per Protocol imm.	47 (58.0)	46 (63.9)	93 (60.8)
HPV 11	46 (56.8)	49 (68.1)	95 (62.1)
HPV 16	47 (58.0)	46 (63.9)	93 (60.8)
HPV 18	48 (59.3)	46 (63.9)	94 (61.4)
HPV 31	46 (56.8)	47 (65.3)	93 (60.8)
HPV 33	48 (59.3)	47 (65.3)	95 (62.1)
HPV 45	50 (61.7)	47 (65.3)	97 (63.4)
HPV 52	49 (60.5)	48 (66.7)	97 (63.4)
HPV 58	48 (59.3)	48 (66.7)	96 (62.7)
SARS-CoV-2 immunogenicity	81	81	162
SARS-CoV-2 Per Protocol	56 (69.1)	60 (74.1)	116 (71.6)

CHMP's comment: the numbers analysed are lower than expected and it creates uncertainty of the magnitude of the seroresponses and AEs.

Efficacy results

The most common reasons for exclusions from either the PPI and/or PP populations were:

• Participant did not receive 2-doses of 9vHPV vaccine or mRNA-1273 vaccine

• Participant was missing serum samples or had samples collected out of range following Dose 2 of 9vHPV vaccine or mRNA-1273 vaccine

• Participant received Dose 2 of 9vHPV vaccine or mRNA-1273 vaccine out of range

• Participant was seropositive to a vaccine-targeted HPV type at Day 1 (PPI population only)

Table 7 - Participants accounting for the Immunogenicity Analysis Population for 9vHPV Vaccine (All Randomised Participants)

	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant (N=82) n (%)	9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant (N=83) n (%)	Total (N=165) n (%)
All randomized participants who received at least 1 9vHPV vaccination	**81**	**72**	**153**
Participants included in Per-Protocol Immunogenicity Population			
HPV 6	47 (58.0)	46 (63.9)	93 (60.8)
HPV 11	46 (56.8)	49 (68.1)	95 (62.1)
HPV 16	47 (58.0)	46 (63.9)	93 (60.8)
HPV 18	48 (59.3)	46 (63.9)	94 (61.4)
HPV 31	46 (56.8)	47 (65.3)	93 (60.8)
HPV 33	48 (59.3)	47 (65.3)	95 (62.1)
HPV 45	50 (61.7)	47 (65.3)	97 (63.4)
HPV 52	49 (60.5)	48 (66.7)	97 (63.4)
HPV 58	48 (59.3)	48 (66.7)	96 (62.7)
Participants excluded in Per-Protocol Immunogenicity Population			
HPV 6	34 (42.0)	26 (36.1)	60 (39.2)
HPV 11	35 (43.2)	23 (31.9)	58 (37.9)
HPV 16	34 (42.0)	26 (36.1)	60 (39.2)
HPV 18	33 (40.7)	26 (36.1)	59 (38.6)
HPV 31	35 (43.2)	25 (34.7)	60 (39.2)
HPV 33	33 (40.7)	25 (34.7)	58 (37.9)
HPV 45	31 (38.3)	25 (34.7)	56 (36.6)
HPV 52	32 (39.5)	24 (33.3)	56 (36.6)
HPV 58	33 (40.7)	24 (33.3)	57 (37.3)
Reason for Exclusion[a]			
Vaccination			
Cross-treated	1 (1.2)	1 (1.4)	2 (1.3)
Did not receive 2 doses of 9vHPV vaccine	14 (17.3)	6 (8.3)	20 (13.1)
Dose 2 of 9vHPV vaccine out of range[b]	5 (6.2)	5 (6.9)	10 (6.5)
Serum Samples			
Predose 1 9vHPV serology result not evaluable for HPV 45	0 (0.0)	1 (1.4)	1 (0.7)
Predose 1 9vHPV serum sample missing or collected out of range[c]	0 (0.0)	3 (4.2)	3 (2.0)
Postdose 2 9vHPV serum sample missing or collected out of range[d]	8 (9.9)	10 (13.9)	18 (11.8)
Postdose 2 9vHPV serology result not evaluable	1 (1.2)	0 (0.0)	1 (0.7)
Other Protocol Deviations			
Received nonstudy HPV vaccine	1 (1.2)	0 (0.0)	1 (0.7)
Day 1 Seropositive			
HPV 6	7 (8.6)	8 (11.1)	15 (9.8)
HPV 11	8 (9.9)	4 (5.6)	12 (7.8)
HPV 16	7 (8.6)	7 (9.7)	14 (9.2)
HPV 18	6 (7.4)	7 (9.7)	13 (8.5)
HPV 31	8 (9.9)	6 (8.3)	14 (9.2)
HPV 33	6 (7.4)	6 (8.3)	12 (7.8)
HPV 45	3 (3.7)	5 (6.9)	8 (5.2)
HPV 52	4 (4.9)	5 (6.9)	9 (5.9)
HPV 58	6 (7.4)	5 (6.9)	11 (7.2)

[a] Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
[b] Day ranges for inclusion in statistical analysis for 9vHPV Dose 2 is 148 to 218 days relative to 9vHPV Dose 1.
[c] Includes participants who received 9vHPV Dose 1 while Predose 1 9vHPV serum sample is missing or collected out of range. Day ranges for inclusion in statistical analysis for Predose 1 serum samples is -14 to 0 days relative to 9vHPV Dose 1.
[d] Includes participants who received 9vHPV Dose 2 while Postdose 2 9vHPV serum sample is missing or collected out of range. Day ranges for inclusion in statistical analysis for Postdose 2 serum samples is 21 to 49 days relative to 9vHPV Dose 2.
N = Number of randomized participants.
The number of all randomized participants who received at least 1 9vHPV vaccination is used as the denominator for the percentage calculation.
cLIA=competitive luminex immunoassay; 9vHPV=9-valent human papillomavirus; mRNA=messenger ribonucleic acid.
PPI=per-protocol immunogenicity.

Source: [P076V503: adam-adsl]

Table 8 - Participants accounting for the Immunogenicity Analysis Population for mRNA-1273 Vaccine (All Randomised Participants)

	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant (N=82) n (%)	9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant (N=83) n (%)	Total (N=165) n (%)
All randomized participants who received at least 1 mRNA-1273 vaccination	**81**	**81**	**162**
Participants included in mRNA-1273 Per-Protocol Population	56 (69.1)	60 (74.1)	116 (71.6)
Participants excluded from mRNA-1273 Per-Protocol Population	25 (30.9)	21 (25.9)	46 (28.4)
Reason for Exclusion[a]			
Vaccination			
Cross-treated	1 (1.2)	1 (1.2)	2 (1.2)
Did not receive 2 doses of mRNA-1273 vaccine	3 (3.7)	3 (3.7)	6 (3.7)
Dose 2 of mRNA-1273 vaccine out of range[b]	7 (8.6)	4 (4.9)	11 (6.8)
Overdose of mRNA-1273 vaccine	3 (3.7)	1 (1.2)	4 (2.5)
Serum Samples			
Predose 1 mRNA-1273 serum sample missing or collected out of range[c]	2 (2.5)	1 (1.2)	3 (1.9)
Postdose 2 mRNA-1273 serum sample missing or collected out of range[d]	13 (16.0)	13 (16.0)	26 (16.0)
Protocol deviations			
Received non-study vaccine 14 days before study vaccination	1 (1.2)	0 (0.0)	1 (0.6)

[a] Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
[b] Day ranges for inclusion in statistical analysis for mRNA-1273 dose 2 is 21 to 42 days relative to mRNA-1273 Dose 1.
[c] Includes participants who received mRNA-1273 Dose 1 while Predose 1 mRNA-1273 serum sample is missing or collected out of range. Day ranges for inclusion in statistical analysis for Predose 1 serum samples is -14 to 0 days relative to mRNA-1273 Dose 1.
[d] Includes participants who received mRNA-1273 Dose 2 while Postdose 2 mRNA-1273 serum sample is missing or collected out of range. Day ranges for inclusion in statistical analysis for Postdose 2 serum samples is 21 to 42 days relative to mRNA-1273 Dose 2.
N = Number of randomized participants.
The number of all randomized participants who received at least 1 mRNA-1273 vaccination is used as the denominator for the percentage calculation.
9vHPV=9-valent human papillomavirus; mRNA=messenger ribonucleic acid; PPI=per-protocol immunogenicity.

Source: [P076V503: adam-adsl]

Based on the results from this study, the following key immunogenicity results were observed:

- Antibody responses to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 following 2 doses of 9vHPV vaccine with the first dose concomitantly administered with the first dose of mRNA-1273 are generally similar to responses following 2 doses of 9vHPV vaccine with the first dose administered alone [Table 9]. The point estimates of [concomitant/nonconcomitant] GMT ratios of anti-HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks following Dose 2 of 9vHPV vaccine ranged from 1.20 to 1.45 depending on the HPV type; the lower bounds of the 95% CIs of the GMT ratios ranged from 0.91 to 1.13.

All (100.0%) PPI-eligible participants contributing to the analysis of immune response following Dose 2 of 9vHPV vaccine seroconverted for each of the 9vHPV vaccine types 4 weeks following Dose 2 of the 9vHPV vaccine in both the concomitant group and nonconcomitant group.

Table 9 - Summary of Anti-HPV cLIA Geometric Mean Titers (Per-Protocol Immunogenicity Population)

Assay (cLIA)	Time Point	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant (N=81)			9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant (N=72)			GMT Ratio (Concomitant vs. Nonconcomitant)
		n	GMT[a] (mMU/mL)	95% CI[a]	n	GMT[a] (mMU/mL)	95% CI[a]	Estimate (95% CI)[a]
Anti-HPV 6	Pre-dose 1	47	< 20	(<20, <20)	46	< 20	(<20, <20)	
	Post-dose 2	47	2,198.5	(1,806.9, 2,674.8)	46	1,806.8	(1,481.8, 2,202.9)	1.22 (0.92, 1.61)
Anti-HPV 11	Pre-dose 1	46	< 16	(<16, <16)	49	< 16	(<16, <16)	
	Post-dose 2	46	1,517.6	(1,247.5, 1,846.2)	49	1,138.2	(941.4, 1,376.2)	1.33 (1.01, 1.75)
Anti-HPV 16	Pre-dose 1	47	< 20	(<20, <20)	46	< 20	(<20, <20)	
	Post-dose 2	47	9,595.8	(7,822.5, 11,771.0)	46	7,042.3	(5,728.2, 8,657.7)	1.36 (1.02, 1.82)
Anti-HPV 18	Pre-dose 1	48	< 24	(<24, <24)	46	< 24	(<24, <24)	
	Post-dose 2	48	2,139.2	(1,721.3, 2,658.6)	46	1,713.2	(1,372.1, 2,139.1)	1.25 (0.92, 1.70)
Anti-HPV 31	Pre-dose 1	46	< 10	(<10, <10)	47	< 10	(<10, <10)	
	Post-dose 2	46	1,695.6	(1,383.9, 2,077.3)	47	1,404.7	(1,149.0, 1,717.2)	1.21 (0.91, 1.61)
Anti-HPV 33	Pre-dose 1	48	< 8	(<8, <8)	47	< 8	(<8, <8)	
	Post-dose 2	48	1,172.3	(950.8, 1,445.5)	47	889.9	(720.2, 1,099.6)	1.32 (0.98, 1.77)
Anti-HPV 45	Pre-dose 1	50	< 8	(<8, <8)	47	< 8	(<8, <8)	
	Post-dose 2	50	518.0	(413.0, 649.6)	47	370.8	(293.6, 468.4)	1.40 (1.01, 1.93)
Anti-HPV 52	Pre-dose 1	49	< 8	(<8, <8)	48	< 8	(<8, <8)	
	Post-dose 2	49	733.6	(614.4, 875.9)	48	504.7	(421.9, 603.7)	1.45 (1.13, 1.87)
Anti-HPV 58	Pre-dose 1	48	< 8	(<8, <8)	48	< 8	(<8, <8)	
	Post-dose 2	48	1,095.2	(900.5, 1,332.1)	48	912.6	(750.3, 1,110.0)	1.20 (0.91, 1.58)

[a] GMTs and 95% CIs, and GMT ratios and 95% CIs are estimated from an ANOVA model with a response of log individual anti-HPV titers and a fixed effect for the vaccination groups.
N = Number of all randomized participants who received at least 1 dose of 9vHPV vaccine.
n = Number of per protocol eligible participants contributing to the analysis.
ANOVA=analysis of variance model; CI=confidence interval; cLIA=competitive luminex immunoassay; GMT=geometric mean titer; 9vHPV=9-valent human papillomavirus; mL=mili liter; mMU=milli Merck units; mRNA=messenger ribonucleic acid.

- Antibody response to SARS-CoV-2 spike protein following 2 doses of mRNA-1273 with the first dose concomitantly administered with the first dose of 9vHPV vaccine is generally similar to the response following 2 doses of mRNA-1273 with the first dose administered alone [Table 10]. The point estimate of [concomitant/nonconcomitant] GMC ratio of SARS-CoV-2 spike protein-specific binding antibody at 4 weeks following Dose 2 of the mRNA-1273 vaccine was 1.17; the associated 95% CI was (0.99, 1.40).

Seroresponse was similar following concomitant (96.4%) and nonconcomitant (95.0%) administration.

Table 10 - Summary of Anti-SARS-CoV-2 Spike Protein Geometric Mean Concentrations (mRNA-1273 Per-Protocol Population)

Time Point	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant (N=81)			9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant (N=81)			GMC Ratio (Concomitant vs. Nonconcomitant)
	n	GMC[a] (U/mL)	95% CI[a]	n	GMC[a] (U/mL)	95% CI[a]	Estimate (95% CI)[a]
Pre-Dose 1	56	23,286.5	(14,903.5, 36,384.9)	60	18,048.8	(11,727.4, 27,777.4)	
Post-Dose 2	56	763,084.3	(673,224.4, 864,938.4)	60	650,527.9	(576,365.9, 734,232.5)	1.17 (0.99, 1.40)

[a] GMCs and 95% CIs, and the GMC ratio and 95% CI are estimated from an ANOVA model with a response of log individual anti-SARS-CoV-2 concentrations and a fixed effect for the vaccination groups.
N = Number of randomized participants who received at least 1 dose of mRNA-1273 vaccine.
n = Number of per protocol eligible participants contributing to the analysis.
ANOVA=analysis of variance model; CI=confidence interval; GMC=geometric mean concentration; 9vHPV=9-valent human papillomavirus; mL=mili liter; mRNA=messenger ribonucleic acid; U=units.

Source: [P076V503: adam-adsl; adam-adimm]

CHMP's comment: the magnitude of the immune responses against HPV and Sars-Cov-2 are comparable when Gardasil 9 and Spikevax are co-administrated or administrated separately.

Safety results

• The overall proportion of participants with any AEs following Dose 1 of 9vHPV vaccine and mRNA-1273 vaccine was generally similar when 9vHPV vaccine and mRNA-1273 vaccine were administered either concomitantly or nonconcomitantly; most events were mild in intensity.

Table 11 - Adverse Event Summary (Days 1 to 28 Following Dose 1)
(All Participants as Treated Population)

	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant		9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant	
	n	(%)	n	(%)
Participants in population with follow-up	81		81	
with one or more adverse events	47	(58.0)	51	(63.0)
injection-site	44	(54.3)	46	(56.8)
non-injection-site	27	(33.3)	36	(44.4)
with no adverse event	34	(42.0)	30	(37.0)
with vaccine-related[a] adverse events	47	(58.0)	51	(63.0)
injection-site	44	(54.3)	46	(56.8)
non-injection-site	25	(30.9)	36	(44.4)
with serious adverse events	0	(0.0)	0	(0.0)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
who died due to a vaccine-related adverse event	0	(0.0)	0	(0.0)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine.
All injection site adverse events solicited from Day 1 through Day 7 postvaccination are considered to be vaccine-related.
Reported adverse events include any adverse events within 28 days of 9vHPV Dose 1 and mRNA-1273 Dose 1 and prior to next vaccination visit, if any.
9vHPV=9-valent human papillomavirus; mRNA=messenger ribonucleic acid.

Source: [P076V503: adam-adsl; adacce]

• The proportion of participants with injection-site AEs 28 days following Dose 1 was generally similar between the concomitant and nonconcomitant groups.

• The proportion of participants with systemic AEs after Dose 1 of mRNA-1273 was generally similar in concomitant and nonconcomitant groups; however, the proportion of participants with solicited systemic AEs after Dose 1 of 9vHPV vaccine was lower when Dose 1 of 9vHPV vaccine was administered nonconcomitantly (16.7%) compared to when Dose 1 of 9vHPV vaccine was administered concomitantly with mRNA-1273 vaccine (33.3%).

This difference was primarily driven by fewer AEs of chills, headache, and nausea following Dose 1 of 9vHPV vaccine alone compared with concomitant administration with mRNA-1273 vaccine (chills 9.9% in the concomitant group; 0% in the nonconcomitant group), headache (22.2% in the concomitant group; 9.7% in the nonconcomitant group), and nausea (7.4% in the concomitant group; 0% in the nonconcomitant group).

Table 12 - Analysis of Participants with Solicited Systemic Adverse Events (Incidence > 0% in One or More Vaccination Groups) (Days 1 to 7 Following Dose 1)

(All Participants as Treated Population)

	9vHPV Vaccine + mRNA-1273 Vaccine Concomitant (9vHPV + mRNA-1273 Dose 1)		9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant (9vHPV Dose 1)		9vHPV Vaccine + mRNA-1273 Vaccine Nonconcomitant (mRNA-1273 Dose 1)		Difference in % vs 9vHPV Dose 1	Difference in % vs mRNA-1273 Dose 1
	n	(%)	n	(%)	n	(%)	Estimate (95% CI)[a]	Estimate (95% CI)[a]
Participants in population	81		72		81			
with one or more adverse events	27	(33.3)	12	(16.7)	30	(37.0)		
with no adverse events	54	(66.7)	60	(83.3)	51	(63.0)		
Solicited systemic adverse event	**27**	**(33.3)**	**12**	**(16.7)**	**30**	**(37.0)**	**16.7 (2.9, 29.9)**	**-3.7 (-18.3, 11.0)**
Arthralgia	4	(4.9)	1	(1.4)	4	(4.9)	3.5 (-3.0, 10.9)	0.0 (-7.8, 7.8)
Chills	8	(9.9)	0	(0.0)	6	(7.4)	9.9 (4.5, 18.3)	2.5 (-6.8, 12.0)
Fatigue	12	(14.8)	5	(6.9)	14	(17.3)	7.9 (-2.4, 18.3)	-2.5 (-14.1, 9.1)
Headache	18	(22.2)	7	(9.7)	22	(27.2)	12.5 (0.8, 24.2)	-4.9 (-18.2, 8.5)
Myalgia	3	(3.7)	4	(5.6)	6	(7.4)	-1.9 (-10.2, 5.6)	-3.7 (-12.1, 4.0)
Nausea	6	(7.4)	0	(0.0)	1	(1.2)	7.4 (2.1, 15.3)	6.2 (-0.1, 14.2)
Vomiting	3	(3.7)	0	(0.0)	2	(2.5)	3.7 (-1.5, 10.4)	1.2 (-5.3, 8.2)

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.
Every participant is counted a single time for each applicable row and column.
Reported adverse events include solicited systemic adverse events within 7 days of (1) 9vHPV Dose 1 + mRNA-1273 Dose 1 at Day 1 for the concomitant group, (2) mRNA-1273 Dose 1 at Day 1 for the non-concomitant group, and (3) 9vHPV Dose 1 at Month 2 for the non-concomitant group, separately.
Arthralgia, chills, fatigue, headache, myalgia, nausea, and vomiting were solicited from Day 1 through Day 7 postvaccination but may have been reported spontaneously after Day 7.
MedDRA version 27.1 was used in the reporting of this study.
9vHPV=9-valent human papillomavirus; CI=confidence interval; mRNA=messenger ribonucleic acid.

Source: 1P076V503: adam-adsl: adaccel

• The proportion of participants with a temperature elevation ≥100.0°F (37.8°C) was generally similar when 9vHPV vaccine was administered concomitantly with mRNA 1273 vaccine and nonconcomitantly.

• Few participants reported MAAEs.

• No SAEs, AESIs, or deaths were reported in the study, and no participant discontinued either study vaccine due to AE.

CHMP's comment: the Spikevax is more reactogenic than Gardasil 9 and therefore the safety profile of co-administration is similar to the SARS-Cov-2 mRNA vaccine safety profile. This is an expected result. As the sample size was low, the probability to discover rare AEs is low.

2.3.3. Discussion on clinical aspects

The results of V503-076 demonstrated that antibody responses following 2 doses of 9vHPV vaccine are generally similar when the first dose of 9vHPV vaccine is administered concomitantly and nonconcomitantly with the first dose of mRNA-1273 vaccine among boys and girls 9- to 11-years-old. The data in this application is consistent with prior findings, demonstrating robust immunogenicity of the 9vHPV vaccine in young adolescents, including when administered with other concomitant vaccinations.

Concomitant administration of the 9vHPV vaccine with the mRNA-1273 vaccine in girls and boys 9- to 11-years-old was generally well tolerated. The safety profile in this study evaluating concomitant and nonconcomitant administration of the 9vHPV vaccine did not reveal any new findings compared with previous studies of the 9vHPV vaccine. Therefore, there were no safety findings that would indicate any change to the safety profile of the 9vHPV vaccine. The benefit to risk ratio of the 9vHPV vaccine continues to be favourable.

The MAH do not propose any changes to the current EU product information for Gardasil 9 from this estimation study with a small sample size, considering that the originally authorized mRNA-1273 vaccine no longer reflects more recent strains of the virus. Also, there is no routine vaccination against Covid-19 in EU among children and the co-administration of Gardasil with Covid-19 vaccine is unlikely to happen. Only in some rare cases among immunosuppressed population this data may be currently relevant, but in this instance, the clinician can ensure that these vaccinations do not happen simultaneously. Therefore the CHMP agrees now, that no update in SmPC is needed. On the other

hand, we encourage the MAH to publish this study to ensure, that this data will be available for the public. These data are relevant as a description of the interaction between different vaccine platforms. Also, in the future, it may happen, that Sars-Cov-2 epidemiology changes and this information may help clinicians to take the decision about co-administration.

3. CHMP overall conclusion and recommendation

The results of this study indicate no new efficacy or safety concerns but provides new valuable information about co-administration of Gardasil 9 and Spikevax (mRNA-1273, 50 µg). As the data was limited and children in EU are not routinely vaccinated against SARS-Cov-2, this information is not seen as essential to be included in Gardasil 9 PI.

☒ **Fulfilled:**

No regulatory action required.